Human Prion Diseases

(Rare Disease of Public Health Significance)

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To monitor trends in the epidemiology of human prion diseases in Washington State.
2. To maximize laboratory confirmation of suspected cases and promote awareness of available resources.
3. To detect the emergence of variant Creutzfeldt-Jakob Disease (vCJD) or novel prion diseases in the United States.
4. To prevent potential iatrogenic transmission.

B. Legal Reporting Requirements

1. Health care providers: **immediately notifiable to local health jurisdiction.**[a]
2. Hospitals: **immediately notifiable to local health jurisdiction.**[a]
3. Laboratories: no requirements for reporting.
4. Local health jurisdiction: **immediately notifiable to the Washington State Department of Health (DOH) Communicable Disease Epidemiology Section (CDES) (206-418-5500 or toll free at 1-877-539-4344).**

[a]In the absence of neuropathological analysis, case definitions for human prion diseases can be complex. The following criteria were developed to identify patients that warrant notification to public health:

- A lack of diagnosed etiological agent and
    - Rapidly progressive dementia with one or more of the following features: movement disorder (i.e., myoclonus, ataxia)**,** visual disturbance**,** pyramidal/extrapyramidal dysfunction**,** akinetic mutism; MRI findings of hyperintense signals in the basal ganglia, thalamus, and cortex on T-2 weighted images; EEG findings of periodic, synchronous sharp-wave complexes superimposed on a slow background rhythm; elevated 14-3-3 protein.
    - Recent onset of cognitive impairment in a younger adult with progressive neuropsychiatric disease, persistent painful sensory symptoms (e.g., dysesthesia), or MRI findings of bilateral pulvinar high signal.
    - Progressive cerebellar or other neurological syndrome in patient with recognized CJD risk factor (e.g., history of human-derived pituitary hormone, dura mater graft recipient, definite or probable prion disease in a first degree relative).

- Or a prion disease suspected by a neurologist or neuropathologist.

C. Local Health Jurisdiction Investigation Responsibilities

1. Encourage providers to discuss the role of autopsy in the diagnosis of prion disease with the patient's family. Inform providers of the autopsy and laboratory services provided by the National Prion Disease Pathology Surveillance Center (NPDPSC).
2. Discuss the importance of appropriate infection control procedures if invasive neurologic diagnostic testing is being considered.
3. Report all *definite, probable, and possible* cases to CDES (see definitions below). Complete the case report form for Human Prion Disease (www.doh.wa.gov/notify/nc/prion.htm) and enter the data into the Public Health Issues Management System (PHIMS) as a Rare Disease of Public Health Significance.
4. Perform a more extensive investigation if variant CJD, iatrogenically transmitted CJD, a novel prion disease, or a disease cluster is suspected.

2. THE DISEASE AND ITS EPIDEMIOLOGY

Background

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a family of rare, fatal neurodegenerative diseases of animals and humans. These diseases have long incubation periods, and cause characteristic spongiform changes, neuronal loss, and gliosis without provoking an inflammatory reaction. Death usually occurs within a year after onset of illness.

The most common prion disease in humans, sporadic Creutzfeldt-Jakob disease (sCJD), occurs worldwide and affects one to two people per million population per year. The risk increases in people over 50 years of age and is higher among whites. Less common prion diseases include Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI).

Animal prion diseases include bovine spongiform encephalopathy (BSE, "mad cow disease") in cattle, scrapie in sheep, chronic wasting disease in deer and elk, and transmissible mink encephalopathy.

A. Etiologic Agent

Prion diseases are thought to result from a change in conformation of normal prion proteins. The term prion is derived from the phrase "proteinaceous infectious particle." In disease, a specific normal cellular protein folds into an abnormal, pathologic form. Prions are resistant to routine physical and chemical sterilization techniques.

B. Description of Illness

Sporadic CJD (sCJD) is a fatal neurodegenerative disease that begins with cognitive and behavioral changes (e.g., memory difficulties) and progresses to include physical neurologic abnormalities (e.g., myoclonus, ataxia, rigidity). Death is often caused by aspiration or sepsis and usually occurs within one year of onset.

In the 1990s, a new variant of CJD (vCJD) was recognized in the United Kingdom (UK). The pathology of vCJD is strikingly similar to that of cattle infected with an animal prion

disease called bovine spongiform encephalopathy (BSE, "mad cow disease"), and consumption of BSE-infected cattle is the likely mode of transmission. In contrast to sCJD, vCJD is characterized primarily by behavioral changes (e.g., psychosis, depression), painful sensory symptoms, a younger age of onset (teens, 20s), and a longer duration of illness. Table 1 shows some of the clinical and pathologic differences between vCJD and sCJD. As of September 2007, more than 200 cases of vCJD have been reported worldwide, mostly in the UK and Europe. In the United States there have not been any reported cases of endemically acquired vCJD though health care providers should be alert for cases in persons who have lived in the UK or Europe.

Table 1: Clinical and pathologic characteristics distinguishing vCJD from sCJD

Characteristic	vCJD	sCJD
Median age at death	28 years	68 years
Median duration of illness	13–14 months	4–5 months
Clinical signs and symptoms	Prominent psychiatric/behavioral symptoms; painful dysesthesia; delayed neurologic signs	Dementia; early neurologic signs
Periodic sharp waves on EEG	Absent	Often present
"Pulvinar sign" on MRI*	Present in >75%	Not reported
Presence of "florid plaques" on neuropathology	Present in large numbers	Rare or absent
Immunohistochemical analysis of brain tissue	Marked accumulation of PrP^{res}†	Variable accumulation
Presence of agent in lymphoid tissue	Readily detected	Not readily detected

*An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery sequences on brain MRI; in the appropriate clinical context, this signal is highly specific for vCJD.

† Protease-resistant prion protein

Source: Centers for Disease Control and Prevention. Creutzfeldt-Jakob disease not related to a common venue—New Jersey, 1995–2004. MMWR 2004;53(18):392–6. Adapted from Belay E, Schonberger L. Variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Clin Lab Med 2002;22:849.

C. Human Prion Diseases in Washington State

Prior to 2005, surveillance for human prion diseases in Washington was primarily conducted by death certificate review. This surveillance method detected 3–9 cases of CJD per year; however, less than half had a laboratory confirmed diagnosis. After implementation of initiatives to improve surveillance with neuropatholgical analysis of brain tissue collected at autopsy, in 2006, seven of nine cases of CJD identified in Washington were laboratory confirmed.

D. Reservoirs

It is unknown whether a reservoir exists for the most common human prion disease, sporadic CJD.

E. Modes of Transmission

The mode of transmission of the most common prion disease in humans, sporadic CJD, is not known. Approximately 10–15% of human prion disease is familial (i.e., inherited) and <1% is acquired through iatrogenic transmission or consumption of BSE infected animal tissues. Rare cases of human prion disease have been acquired during medical procedures from contaminated human-derived pituitary hormones, dura mater grafts, corneal grafts or neurosurgical equipment.

Acquisition of vCJD has been associated with consumption of beef products contaminated with the bovine spongiform encephalopathy (BSE or "mad cow disease") agent and food protection measures have been implemented to prevent meat products from suspected or confirmed BSE infected cattle from being sold for consumption. Three recent cases of vCJD in the United Kingdom provide evidence for transmission of this disease through blood transfusion, however other human prion diseases are not known to be transmitted by transfusions. Prion diseases of humans are not transmitted through casual or intimate person-to-person contact.

F. Incubation Period

The incubation period for the few prion diseases with known sources (i.e., vCJD, iatrogenically-acquired prion disease) is variable and extremely long, in the order of several years to decades.

G. Period of Communicability

There is no evidence that any prion disease is transmitted through casual or intimate person-to-person contact. In general, there is no communicability, however in very rare circumstances, CJD has been acquired by contaminated neurosurgical instruments, transplanted dura mater and corneas, human-derived pituitary hormones, and possibly for vCJD only, in transfused blood.

H. Treatment

There is no curative treatment; these diseases are invariably fatal. Supportive care is needed and medications may be used to control aggressive or agitated behaviors.

3. CASE DEFINITIONS

Notes:

- *This is a group of distinct diseases rather than a single disease. Although all human prion diseases are reportable, the case definitions below describe various forms of CJD.*
- *Criteria to identify patients that warrant notification to public health are listed in section 1B.*
- *The word "definite" is used instead of "confirmed" to conform to the World Health Organization's case definition.*

A. Sporadic CJD[b]

1. **Definite:** Neuropathological confirmation; and/or confirmation of protease-resistant prion protein by immunohistochemistry or Western blot; and/or presence of scrapie-associated fibrils.
2. **Probable:**
   - Progressive dementia; and
   - At least two out of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal/extrapyramidal signs, or 4) akinetic mutism; and
   - A typical EEG during an illness of any duration; and/or a positive 14-3-3 CSF assay with clinical duration to death of <2 years; and
   - The absence of an alternative diagnosis.
3. **Possible:**
   - Progressive dementia; and
   - At least two out of the following four clinical features: 1) myoclonus, 2) visual or cerebellar signs, 3) pyramidal/extrapyramidal signs, or 4) akinetic mutism; and
   - EEG atypical or not known; and
   - Clinical duration to death <2 years.

B. Iatrogenically Transmitted CJD[b]

1. **Definite:** Definite CJD with a recognized iatrogenic risk.
2. **Probable:** Progressive cerebellar syndrome in a recipient of human-derived pituitary hormone; or probable CJD with a recognized iatrogenic risk, e.g., antecedent neurosurgery with dura mater implantation.

C. Familial Prion Diseases[b]

1. **Definite:** Definite prion disease with a recognized pathogenic PrP mutation and definite or probable prion disease in a first-degree relative.
2. **Probable:** Probable prion disease *and* definite or probable prion disease in a first-degree relative; **or** a progressive neuropsychiatric disorder *and* disease-specific genetic mutation.

D. Variant CJD[b]

1. **Definite:** Neuropathologic confirmation of vCJD with a progressive neuropsychiatric disorder.
2. **Probable:**
   - Progressive neuropsychiatric disorder, duration of illness >6 months, absence of an alternative diagnosis, no history of potential iatrogenic exposure, no evidence of familial CJD and
   - 4 of 5 of the following symptoms: 1) early psychiatric symptoms 2) persistent painful sensory symptoms 3) ataxia 4) myoclonus or chorea or dystonia 5) dementia and
   - EEG absent or does not show typical appearance of sporadic CJD and
   - MRI brain scan shows bilateral symmetrical pulvinar high signal.

     OR

   - Progressive neuropsychiatric disorder, duration of illness >6 months, absence of an alternative diagnosis, no history of potential iatrogenic exposure, no evidence of familial CJD and
   - A positive tonsil biopsy.
3. **Possible:** Progressive neuropsychiatric disorder, duration of illness >6 months, absence of an alternative diagnosis, no history of potential iatrogenic exposure, no evidence of familial CJD and 4 of 5 of the following symptoms: 1) early psychiatric symptoms 2) persistent painful sensory symptoms 3) ataxia 4) myoclonus or chorea or dystonia 5) dementia and EEG absent or does not show typical appearance of sporadic CJD.

[b] World Health Organization Communicable Disease Surveillance and Response. WHO Manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt-Jakob disease. Geneva, Switzerland: 2003.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

Confirmatory diagnosis of prion diseases requires laboratory examination of brain tissue. The importance of autopsy and laboratory testing should be discussed with the patient's family. Arrangements for autopsy and laboratory testing can be made through the National Prion Disease Pathology Surveillance Center (contact information below). This national reference center provides state-of-the-art prion disease diagnostics, including histopathology, immunohistochemistry, Western blot, and genetic analysis to confirm and determine the type of prion disease. These services are offered free of charge.

Antemortem indicators are not confirmatory. Antemortem indicators that support but cannot confirm the diagnosis of CJD include certain findings on EEG and MRI (see Table 1) and elevated levels of 14-3-3 protein in cerebral spinal fluid (CSF). Testing CSF for the protein marker 14-3-3 may be helpful in patients exhibiting rapidly progressive dementia, however the 14-3-3 marker is not specific or diagnostic for sCJD, and sensitivity decreases as the illness progresses. The 14-3-3 immunoassay is not a

screening test and should be used only when a diagnosis of CJD is strongly suspected. The NPDPSC performs 14-3-3 immunoassays free of charge.

B. Services Available at DOH Public Health Laboratories (PHL)

PHL does not perform diagnostic testing for prion diseases. All specimens should be sent directly to the NPDPSC.

C. Specimen Collection

For details regarding the collection and shipment of clinical specimens, see the NPDPSC website (http://www.cjdsurveillance.com) or call (216) 368-0587.

5. ROUTINE CASE INVESTIGATION

Cases of possible, probable, and definite prion disease are primarily identified from three sources: 1) reports from health care providers; 2) NPDPSC lab reports; and 3) death certificates.

A. Evaluate the Diagnosis

1. Determine the status (alive or deceased) of the patient. There is no need to interview the next of kin unless vCJD, iatrogenically transmitted CJD, a novel prion disease, or a disease cluster is suspected.
2. Interview the provider and/or review medical records to collect information on the patient's clinical presentation and antemortem test results (see above). See Appendix A for definitions of neurologic terms found on the case report form.
3. If the patient is alive but not expected to survive, strongly encourage the provider to discuss the essential role of autopsy for diagnosis with the patient's family. If the family consents to having an autopsy performed, they should complete the NPDPSC autopsy consent form (available at http://www.cjdsurveillance.com/pdf/consent-autopsy.pdf) and send or fax it to the NPDPSC. All arrangements and expenses including transport of the body to a facility that can perform a brain-only autopsy, collection of brain tissue, return of the body, and specimen shipping and testing are covered by the NPDPSC. NPDPSC is the national reference laboratory for human prion diseases that performs advanced neuropathologic and biochemical diagnostics, including histopathology, immunohistochemistry, Western blot, and prion gene analysis to confirm the diagnosis of prion disease and distinguish the type (e.g., familial vs. sporadic).
4. If the patient is deceased, determine the date of death and whether brain tissue has been collected postmortem for laboratory testing. Ascertain which laboratory has the tissues and forward any pathology report with the case report form.

B. Identify Potential Sources of Infection

Ask the provider if the patient ever received human-derived pituitary hormones (especially human-derived growth hormone), dura mater or corneal grafts, had a neurosurgical procedure, or is biologically related to a person with heritable prion disease.

If a patient is suspected to have iatrogenically-acquired prion disease, vCJD or another novel acquired prion disease, contact CDES. An extensive investigation including an interview with the next of kin will need to be initiated.

C. Identify Potentially Exposed Persons

Determine if the patient had a neurosurgical procedure during this illness. If so, contact CDES. The hospital where the procedure was performed should be contacted to determine if equipment, surfaces, and other objects were properly decontaminated.

D. Environmental Evaluation

None.

6. CONTROLLING FURTHER SPREAD

A. Infection Control Recommendations

1. Standard precautions are recommended for hospitalized patients; additional special precautions are necessary during invasive neurosurgical or ophthalmic procedures.
2. Neurosurgical procedures: The brain, spinal cord and eyes of patients with prion disease are highly infectious and prions are resistant to routine physical and chemical sterilization methods used in medical facilities. As a result, neurosurgical equipment, surfaces and other objects in contact with nervous tissue or eyes of a person with a prion disease require special decontamination procedures. If a patient with confirmed or suspected prion disease requires or recently had a neurosurgical procedure or invasive EEG monitoring, please contact the facility's infection control division so that appropriate infection control measures can be implemented. Information about infection control measures related to CJD is available from the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dvrd/cjd/qa_cjd_infection_control.htm) and the World Health Organization (WHO) (http://whqlibdoc.who.int/publications/2003/9241545887.pdf).
3. Autopsy: The World Health Organization (WHO) Infection Control Guidelines for Transmissible Spongiform Encephalopathies should be followed during autopsy of a patient with confirmed or suspected human prion disease. WHO's infection control guidelines can be found at: http://whqlibdoc.who.int/publications/2003/9241545887.pdf.
4. Embalming: The Centers for Disease Control and Prevention guidelines 'Information on Creutzfeldt-Jakob Disease for Funeral Home, Cemetery and Crematory Practitioners' should be followed (see http://www.cdc.gov/ncidod/dvrd/cjd/funeral_directors.htm).
4. Tissue/Organ Donation: Tissues and organs from patients with confirmed or suspected prion disease should not be donated for transplantation or teaching purposes.

Note: Additional infection control measures are recommended in some circumstances for persons 'at risk' for developing prion disease. These persons are defined as asymptomatic persons who meet any of the following criteria: 1) received dura mater ***or*** human-derived pituitary hormones, especially human-derived growth hormone ***or*** cornea transplants, 2) have undergone neurosurgery, or 3) are members of families with heritable prion disease.

Source: World Health Organization Communicable Disease Surveillance and Response. WHO Manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt-Jakob disease. Geneva, Switzerland: 2003.

B. Case Management

If routine case investigation activities have been completed, no case follow-up is needed after an autopsy is arranged. Once pathology results are available, the case can be classified. NPDPSC provides pathology test results to the physician and CDES who, in turn, will send the results to the local health jurisdiction.

C. Contact Management

No follow-up is needed for close contacts of the patient since there is no evidence that any human prion disease is transmitted through casual or intimate person-to-person contact. If you suspect a patient had a neurosurgical procedure when the hospital was unaware of the suspected prion disease status, contact CDES.

D. Environmental Measures

If a neurosurgical procedure has been done, see Infection Control section above.

7. ROUTINE PREVENTION

A. Immunization Recommendations

There is no vaccine to prevent human prion diseases.

B. Prevention Recommendations

There are no prevention measures for the majority of human prion diseases. See the infection control section above for precautions in hospital and other special settings.

APPENDIX A

The following terms and their definitions may assist with the questions on the prion disease case report form and terms that you may find during CJD chart reviews.

- Akinetic mutism: Akinetic mutism is the loss of the voluntary ability to speak and move. This term should be specifically stated. Unless it is clearly stated that the patient is awake and not comatose, do not substitute the term "unresponsive."
- Cerebellar signs of CJD may include:
    - Ataxia: failure of muscular coordination. Affected patients have coordination, postural and balance problems early in the disease process and as the disease progresses, severe ataxia leads to loss of ability to walk.
    - Opsoclonus (horizontal and vertical oscillations of the eyes)
    - Nystagmus (involuntary rapid rhythmic movement of the eyeball)
    - Truncal titubation / truncal ataxia (staggering, stumbling gait with shaking of the trunk)
    - Appendicular ataxia (lack of coordination in a limb)
    - Movement tremor (involuntary trembling/quivering)
    - Termination or terminal tremor would be included in CJD signs, however "tremor" alone is not necessarily a cerebellar or CJD sign.
- Chorea: Writhing movements of the body / extremities. Rapid, highly complex jerky movements that appear to be well coordinated but occur involuntarily.
- Dementia: Dementia refers to cognitive decline.
- Dysesthesia and painful sensory symptoms: New onset of pain or other uncomfortable sensations that is unrelated to injury or stimulus.
- Dystonia: Abnormal tonicity in muscles resulting in impairment of voluntary movement.
- Hyperreflexia: Exaggerated reflexes
- Myoclonus: Sudden, involuntary contractions or jerking of a muscle or group of muscles. Terms such as "myoclonic jerks", "myoclonic jerking", "myoclonic activity" are also acceptable. These variants of myoclonus may be mentioned:
    - Nocturnal myoclonus
    - Facial myoclonus
    - Action myoclonus
    - Startle myoclonus

    Terms such as "twitching", "tremulousness", or "shaking / shakiness" are not equivalent and the term "clonus" represents a separate neurologic sign.

- Progressive Dementia: Ongoing cognitive decline. The development of dementia in CJD patients is very pronounced over a short period of time (weeks) unlike dementia associated with Alzheimer's disease. Terms like "delirium", "altered mental status", or "unresponsiveness" should not be interpreted as representing progressive dementia, unless there is clear evidence in the chart that the condition has been ongoing for weeks / months and that the patient is progressively getting worse in terms of cognitive ability.
- Progressive neuropsychiatric disorder: Abnormalities in the nervous system and in mental processes. In the variant form of CJD, the first symptoms are psychiatric and patients experience a progressive neuropsychiatric disorder lasting at least 6 months. In the sporadic form, if neuropsychiatric disorders are present, they usually are concurrent with the physical manifestations of the disease.
- Pyramidal signs refer to disorders of the upper motor neuron pathway going from the motor cortex through the brainstem and down to the spinal cord. Pyramidal signs would include things such as:
    - Upper motor neuron weakness
    - Hemiplegia (paralysis of one side of the body)
    - Spastic (limb) paralysis / paresis
    - Hyperreflexia
    - Presence of Babinski's sign / "upgoing toes"
    - Spasticity
    - Clonus (alternate muscular contraction and relaxation in rapid succession)
- Extrapyramidal signs refer to disorders of brain structures controlling movement; mainly with reference to the basal ganglia and related structures. The most commonly recognized extrapyramidal signs are those that we associate with Parkinson's disease. Extrapyramidal signs of CJD may include:
    - Bradykinesia / hypokinesia (slowness of movement)
    - Rigidity (limb or neck)
    - Tremor
    - Hypomimia (flat facies, masked facies, lack of facial expression)
    - Postural instability
    - Shuffling gait
    - Ballismus / hemiballismus (sudden flinging movements of the extremities)
    - Chorea / choreoathetosis (writhing movements of the body / extremities)
- Visual Deficits: The visual abnormalities in CJD most commonly are complex visual disturbances, such as hallucinations or cortical blindness. Do not count terms such as "blurred vision" or "decreased visual acuity." Terms that may be to describe CJD-associated visual deficits include the following:

- Visual hallucinations
- Hemianopsia (defective vision or blindness in half of the visual field)
- Visual field cut / visual field deficit
- Blindness
- Opsoclonus (horizontal and vertical oscillations of the eyes)
- Diplopia / double vision